REMARKS

Claims 13 through 34 have been withdrawn. Original claims 1, 2, 4, 6, 9, 10, and 11 have been amended to improve form. New claims 35-42 have been added.

Claims 10 and 11 have been amended pursuant to the Examiner's rejection under 35 U.S.C. § 112, second paragraph contained in paragraph 5 of the Office Action.

With respect to the comments made by the Examiner in paragraphs 2 through 5 of the Office Action, it is respectfully submitted that each of the items addressed by the Examiner has been corrected as requested by the Examiner. The title has been changed, trademarks are corrected, and reference to the priority documents has been added.

Rejection of Claims 1-2, and 4-12

The Examiner at paragraph 7 of the Office Action rejects Applicants' claims 1-2,and 4-12 under 35 USC §103(a) as being unpatentable over Curiel et al. (U.S. Patent No. 6,284,742) (829; of record) in view of Xiang et al. (J. Immunol. 167: 4560-4565, 2001) (1449; #A91), Zheng et al. (Cancer Research 61: 8127-8134m, 2001) (1449; #A96), Hu et al. (PNAS 96: 8161-8166, 1999), Dreyfus et al. (US 2002/0068048), and Thomas et al. (US 2005/0048645).

As to the rejection of claims 1-2, and 4-12, it is respectfully submitted that Applicants first note that the Examiner has used a total of six references, to attempt to indicate that claims 1, 2, and 4-12 are somehow obvious. More particularly, the Examiner has taken a selected teaching from each of the six references, and combined the teachings for alleging a rejection on the basis of obviousness. The Office Action apparently dismisses many of the material distinctions between the references, one from the other and the material distinctions of each reference from Applicants' invention defined by claims 1, 2 and 4-12, which differences are outlined in detail below.

It is respectfully submitted that the rejection is a piecemeal combination of teachings, without any objective justification for such an alleged reconstruction of Applicants' invention.

Further, it is submitted that there is no motivation, in any one or more of the references, to support a rejection of obviousness, based on the combination of the six cited references, to render claims 1, 2 and 4-12 as obvious.

As further reflected in the following detailed accounting for each of the six cited references, each such reference is directed to not only a different invention but a different conceptual approach, as opposed to the invention recited in claims 1, 2 and 4-12. These six different conceptual approaches, whether taken singularly or collectively, each teach away from Applicants' invention and from each other. There also appears to be no primary reference utilized by the Examiner as a basis for substituting a teaching from each of the remaining five references thereby also raising a serious question as to a proper foundation for the obviousness rejection.

The reconstruction of Applicants' invention from varying technology approaches is respectfully submitted to be no more than a hindsight reconstructed combination based solely upon Applicants' specification. In fact, it is respectfully submitted that based upon the absence of any supported objective justification or reasoning in the Office Action for combining the six teachings, where the selection of each teaching is taken out of context from each of six disparate references, and where no one of the dissimilar and conflicting prior art references discloses any motivation for use as a reference to in combination with the other five references, that such unsupported obviousness rejection, by itself, underscores the very novelty of Applicants' invention as claimed. Each of the applied references with respect to claim 1 as well as a number of other of Applicant's claims are discussed in detail below.

Curiel, et al. - With respect to the cited prior art, Curiel, et al., according to the Office Action, teaches recombinant adenoviral vectors, comprising CD40L and a tumor or infectious agent antigen to manipulate the immune response. The Office Action, however, acknowledges that Curiel is different from Applicants' claimed invention in that Curiel et al. fails to explicitly describe all of the claimed properties of the claimed adenoviral expression vector, including that the CD40 ligand is missing all or substantially all of the transmembrane domain rendering the CD40L secretable, as recited in claim 1.

Yet, clearly, Curiel et al., also differs in other respects from features recited in claim 1. For example, Curiel et al. is focused on placing CD40L on the surface of the viral coat protein as

a ligand to promote binding and entry of adenoviral vectors into dendritic cells or antigen presenting cells. As acknowledged by the Examiner, the CD40 ligand recited in claim 1 is missing all or substantially all of the transmembrane domain rendering the CD40L protein secretable, which is not present in Curiel et al. Accordingly, employing Curiel, et al.'s approach of placing CD40L on the surface of the viral coat protein (outside the vector), as opposed to Applicants' attaching the target antigen to the extracellular domain of the CD40L, in the transcription unit of an adenoviral expression vector designed to infect and program any type of cell to release tumor antigen/CD40L fusion proteins from the vector infected cells, and to manipulate the immune response, is a diametrically opposed approach employing a different technology.

More specifically, to take the adenoviral vector teaching out of Curiel , et al., used in a different manner and approach than that recited in claim 1, is taking a teaching from Curiel, et al. out of context in connection with Curiel, et al.'s intended inventive purpose. It is respectfully submitted that use of the Curiel, et al. CD40L teaching in a manner not contemplated by Curiel, et al. is not a proper application or motivation for use of a teaching.

Moreover, as opposed to Curiel, claim 1 recites that the CD40L is rendered secretable. This secretion, in turn, will promote expression of the tumor antigen on Class I MHC (Major Histocompatibility Complex) proteins on dendritic cells (see, for example, claim 2) and where dendritic cells, in turn, are caused to migrate to lymph nodes where they activate and induce expansion of antigen specific CD8 effector T cells (see, for example, new claims 37, 39 and 40-42), whereby the problem of presenting tumor antigens on Class I MHC of dendritic cells is solved in a very effective way, thereby overcoming the states of anergy and defective T cell helper function in immunocompromised signals. This solution is not taught in any one of the references including Curiel et al. In generating an immunity against a human tumor antigen, human dendritic cells will encounter, activate and cause expansion of cytotoxic CD8 T cells against the tumor antigen positive cancer cells (see again, for example, amended claim 2 and new claims 37, 39 and 40-42).

Xiang et al. - Xiang et al., according to the Office Action, employs the teaching of a dual-function DNA vaccine encoding a tumor antigen and CD40L ligand trimer. However, Xiang et al. does not teach an adenoviral expression vector carrying a transcription unit which

encodes a fusion protein in which the amino terminal end of the ecdCD40L is linked to the tumor antigen as set forth in claim 1. Xiang et al. instead creates a bacterial plasmid vector comprised of fusion of the carboxyl terminus of CD40L with target antigens which, in Xiang's invention, notwithstanding any language in Xiang et al. to the contrary, prevents the binding of the CD40L to the CD40 receptor. See at page 4561 of the Xiang et al. article, where it states under the heading "Construction of Expression Plasmas", that "...the plasmid pCD40LT-CEA contains the entire CEA extracellular domain fused to the C terminus of murine CD40L,...". In contrast, claim 1 recites an adenoviral expression vector comprising a transcription unit encoding a polypeptide, where said polypeptide comprises from the amino terminus, a secretory signal sequence, a tumor antigen and a CD40 ligand, thereby leaving the carboxyl terminus of the CD40L free to bind to the CD40 receptor on dendritic cells.

Further, claim 1 is distinct from Xiang et al. in that in Xiang et al., the transmembrane is not addressed as being removed thereby not rendering, in Xiang et al., the CD40L fusion protein secretable as recited in claim 1. See again the Xiang et al. article on page 4561 under the heading "Construction of Expression Plasmids" at the last three lines stating that the entire extracellular CEA is fused to the CD40L C terminus of murine CD40L. As stated, it is perfectly clear that connection is to the entire murine which includes the full transmembrane. Similarly, see the Xiang et al. U.S. Patent No. 6,923,958 at column 12 lines 32-35. Figures 8 and 9 of the patent illustrate the full human and murine CD40L containing the entirety of the transmembrane domain. Discussion at column 11 at lines 1-40 of the Xiang et al. patent suggest possible alterations but only those which result in a silent change, thus producing functionality equivalent CEA and/or CD40 ligand proteins. In other words alterations are not suggested that conceptually change Xiang et al. as exemplified in the specification. Nowhere, in Xiang et al., is there any disclosure addressing the CD40 ligand missing all or substantially all of the transmembrane domain thereby rendering the CD40L is secretable as is called for in claim 1.

These completely different technical approaches are very significant. Using a selected teaching of Xiang out of context in a different manner than contemplated by the Xiang reference, which employs a much different technical approach than recited in claim 1, is respectfully submitted to be an improper use of a teaching (in combination with other teachings also used in

a different manner than used in their respective disclosures) for rendering claim 1 as unpatentable on the basis of obviousness.

Applicants' claim 4 more specifically recites a transcription unit encoding a linker between the tumor antigen and the amino terminus of said CD40 ligand thereby leaving the carboxyl terminus to bind to a CD40L receptor, which, as stated above, is not found in Xiang. In addition, because of the difference in Applicants' technical approach from Xiang, the above noted binding of the CD40L to the CD40 receptor will, as recited in claims 2, 37, 39 and 40-42, further result in activation of said dendritic cells which are then caused to present the tumor antigen on and Class I MHC thereby overcoming the states of anergy and defective T cell helper function in immunocompromised signals.

Zheng et al. - While Zheng et al. according to the Office Action teaches the use of fusion proteins, Zheng et al. teaches the use of the extracellular domain of CD40L for the induction of antitumor immunity. However, Zheng et al.'s invention is distinct from claim 1 in that Zheng et al. teaches the painting of the outer surface of the tumor cell using the complex system of two fusion proteins for the attachment of activators of a non-antigen specific immune response to the tumor cells since the invention of Zheng et al. specifies the attachment of several immunostimulatory signals which are not antigen-specific (see at page 8127 of Zheng et al. under the Abstract at lines 8-19). In contrast with Zheng et al.'s invention, claim 1 calls for an adenoviral expression vector comprising a transcription unit encoding a polypeptide, said polypeptide comprising from the amino terminus a secretory signal sequence, a tumor antigen, and a CD40 ligand that is missing all or substantially all of the transmembrane domain rendering the CD40L secretable to induce an immune response against a tumor antigen and therefore is antigen specific.

Zheng et al. further fails to teach use of an adenoviral expression vector carrying a transcription unit encoding the tumor antigen/ecdCD40L protein, the release of the protein from vector infected cells, which proteins activate and antigen load dendritic cells so that they are caused to migrate to lymph nodes where they encounter, activate and expand antigen specific CD8 effector T cells (see, for example, new claims 37, 39 and 40-43), in effect, solving the problem of presenting tumor antigens on Class I MHC (see claim 2) by overcoming states of anergy and defective T cell helper function in immunocompromised subjects. Zheng et al.

additionally fails to teach a transcription unit, of an adenoviral expression unit, encoding a linker between the tumor antigen and the amino terminus of a CD40 ligand as recited in claim 4. Yet further, Zheng et al. further fails to teach where the vector, of an adenoviral expression vector, is rendered non-replicating in normal human cells as recited in claim 12.

Thomas et al. - Thomas et al. according to the Office Action teach the soluble CD40L, including the extracellular domain region of CD40L or fusion proteins comprising the extracellular domain of CD40L is sufficient for stimulating immune response of interest. Yet Thomas et al.'s invention is quite distinct from that of Applicants in that Thomas et al. teaches development of in vitro admixtures of extracts of the yeast Cryptococcus neoformans with DCs and CD40L for the use of administration of such mixtures to human subjects for the purpose of stimulating an immune response to yeast. The goal of Thomas et al. appears to be to have the CD40L (soluble CD40L) to add to the inventors' mixture of dendritic cells, and cryptococcus neoformanns antigen. Thomas et al. fails to teach such a use with an adenoviral expression vector carrying a transcription unit encoding a secretable tumor antigen/ecdCD40L, as recited in claim 1. Moreover, the Examiner states that Thomas et al. also teach "the soluble CD40L" which is respectfully submitted to obviously be quite distinct from a CD40L rendered secretable as set forth in claim 1.

The environment in which the Thomas et al. invention operates is completely different than that of Applicants. For example, the recitation in claim 2 of the tumor antigen being connected to the amino terminus of the CD40L to render the CD40L secretable to promote presentation of the tumor antigen on Class I MHC of human dendritic cells is absent in Thomas et al.. Also, the recitation in claim 4 of a transcription unit encoding a linker between a tumor antigen and the amino terminus of the CD40 ligand is absent from Thomas et al. Further, Thomas et al. fails to disclose an adenoviral expression vector where its transcription unit encodes a tumor antigen/ecdCD40L protein which is secretable from infected cells and where the vector is rendered non-replicating in normal human cells as stated in claim 12. Yet further, Thomas et al. additionally fails to teach activating dendritic cells to migrate to lymph nodes for binding with T cells (see, for example, new claims 37, 39, and 40-42), for solving the Class I MHC problem.

Hu et al. - Hu, et al. according to the Office Action teaches the same or nearly the same adenoviral vectors for delivery of cancer modulators of interest. The Examiner acknowledges, however, that Hu et al. fails to teach the use of CD40L as immunotherapy treatment for cancer with targeting. Hu et al. teaches the intratumoral injection of adenoviral vectors carrying a transcription unit encoding a factor VII/IgGFc fusion protein for the purpose of destroying tumor vasculature. This is quite dissimilar from Applicants' invention calling for a replication incompetent adenoviral expression vectors carrying a transcription unit which encodes a secretable CD40L protein as recited in claim 1 and which vector is replication incompetent as recited in claim 12, which encodes the cells it infects to release the CD40L protein. In fact, Hu et al's invention is designed to activate the innate immune response (not a tumor antigen specific immune response) for the purpose of promoting the binding of antigen non-specific natural killer cells (see in Hu et al. in the Abstract at lines 7-9) and complement to the luminal membrane of tumor vascular endothelial cells. In contrast, Applicants' invention is designed to generate immunity against a tumor antigen as recited in claim 1.

Hu et al. additionally fails to teach or address the use of an adenoviral expression vector carrying a transcription unit which encodes a secretable CD40L protein which encodes the cells it infects to release the CD40L protein for the purpose of binding antigen loaded TAA on Class I MHC of the dendritic cells as recited in claim 2, followed by migration of the dendritic cells to the lymph nodes for the purpose of encountering, activating, and expanding TAA specific CD8 effector T cells (see for example, new claims 37, 39 and 40-42). Further, Hu et al. fails to disclose a transcription unit of an adenoviral expression vector encoding a linker between a tumor antigen and the amino terminus of a CD40 ligand as recited in claim 4.

Dreyfus, et al. - As to the sixth reference, Dreyfus et al., the Office Action states that Dreyfus teaches the advantages of viral vectors such as adenovirus for efficient delivery of nucleic sequences coding for a secretable therapeutic peptides. However, Dreyfus et al. states that the Dreyfus et al. invention is directed to the use of loading monocytes with the "therapeutic cargo" followed by intravenous injection of the loaded monocytes into test subjects for the purposes of delivery of said monocytes to the tissue of the central nervous system for the purpose of treating CNS disease. There is no discussion in Dreyfus et al. of the use of adenoviral

expression vectors carrying CD40L transcription units for the purpose of promoting TAA/ecdCD40L secretable fusion proteins, as recited in claim 1.

In fact, Dreyfus does not teach the use of adenoviral vectors for delivery of therapeutic molecules but teaches the use of monocytes for delivery of therapeutic cargo (see Dreyfus sections 006-007, 0013, 0015, and 0080). Therefore, Dreyfus uses adenoviral vectors for the loading of monocytes with one type of therapeutic cargo, DNA transcription units, so that the monocytes can deliver these therapeutic cargo to the central nervous system by the homing of the monocytes through the blood stream to the tissue target (see Dreyfus sections 0025, 0041, and 0097). Applicants' claim 1, in contrast, recites the use of adenoviral expression vectors for the delivery of the TAA/CD40L to the human body, and ultimately to the antigen presenting cells (dendritic cells) in order to generate immunity to tumor antigen.

Further, Dreyfus does not teach where a transcription unit of an adenoviral expression vector encodes a linker between the tumor antigen and the amino terminus of a CD40 ligand as recited in claim 4. Nor does Dreyfus et al. teach where the vector of an adenoviral expression vector is rendered non-replicating in normal human cells as recited in claim 12. In addition, Dreyfus fails to show where an adenoviral expression vector carrying tumor antigen/CD40L transcription unit is designed to induce the release from vector infected cells tumor antigen/CD40L secretable fusion proteins for inducing a systemic tumor antigen specific CD8 effector T cell mediated anti-tumor adaptive immune response (or even infections for that matter) as stated in claims 37, 39, 40-42, by further promoting presentation of the tumor antigen on Class I MHC of human dendritic cells as recited in claim 2.

Summary - With respect to original claim 1, the Examiner has taken teachings from six disparate references out of context, none of which taken singly or in combination discloses or suggest each of the features recited in claim 1. The Office Action then summarizes by combining the six teachings, out of context, to somehow allegedly arrive at the invention recited in claim 1. The Applicants respectfully submit that such a combination of references is not a legitimate combination of references. The Applicants further submit that the Office Action does not clearly explain how (in their combination) the Examiner would change the characteristics and utilization of these different teachings from their use in the respective inventions in which

these teachings were originally employed. For example, the soluble CD40L taught in Thomas et al. is different from the CD40L employed in the applicants' invention.

The Office Action further fails to lay any objective foundation or reason for the motivation to combine the teachings, which teachings Applicants contends either fail to teach what the Examiner suggests or the teachings are inapplicable in the manner applied by the Examiner. It appears that the Examiner is merely using hindsight reasoning with these combined teachings (which Applicants maintain are not combinable for the reasons advanced above) after having read Applicants' invention.

In fact, it would appear that using the teachings of any one of the references cited in the Office Action, if inserted into any one of the other prior art references, would not only appear to completely destroy the invention of any such reference (and goal or purpose of any such reference), but would amount to creating a different invention (the operation or use of which would be questionable at best) and still would fall far short of recreating the invention recited in claim 1 or rendering claim 1 as obvious. Even more interesting, it is of note that some of the references do not even refer to a tumor antigen (see, for example, Zheng et al., Thomas et al., Hu et al., and Dreyfus et al.).

Clearly, considering all the Examiner's evidence, such evidence, in itself, is submitted to underscore the position (contradictory to the Examiner's position of obviousness), that claim 1 is unobvious. Indeed, not one of the six cited references can be used as a primary reference for expressly disclosing a adenoviral expression vector, for generating immunity against a tumor, having a transcription unit rendering a secretable TAA/ecdCD40L protein as set forth in claim 1. These claimed features lead to solving the long standing problem in tumor immunotherapy (as presented in further claims) of promoting the presentation of TAA on Class I MHC of dendritic cells overcoming the states of anergy and defective T cell helper function in immunocompromised individuals. A very effective solution for this problem has eluded researchers for decades. In effect, Applicants' invention results in the expansion of TAA specific CD8 effector T cells even in immunocompromised individuals. None of the prior art cited by the Examiner has taught these features as reflected in Applicants' claims. (See, for example, sections 0014, 0018, 0041, 0042, 0044, 0045, 0047, 0074, and 0076-0078). For at least the reasons discussed above, withdrawal of the rejection and allowance of claim 1 are respectfully requested.

More particularly, with respect to amended claims 2, 4, 6, 9, 10 and 11, and original claims 5, 7, 8 and 12, these claims depend from claim 1, and accordingly are also submitted not to be obvious and not to be anticipated by the prior art for the reasons advanced above.

Rejection of Claim 3

The Examiner at paragraph 8 of the Office Action rejects claim 3 under 35 USC § 103(a) as being unpatentable over Curiel et al. (U.S. Patent No. 6,284,742) (892; of record) in view of Xiang et al. (J. Immunol. 167: 4560-4565, 2001) (1449; #A91), Zheng et al. (Cancer Research 61: 8127-8184, 2001) (1449; #A96), Hu et al. (PNAS 96: 8161-8166, 1999), Dreyfus et al. (US 2002/0068048), and Thomas (US 2005/0048645) as applied to claims 1-2 and 4-12 above and further in view of Lamikanra et al. (J. Virol. 75: 9654-9664, 2001) (1449: #A63).

Lamikanra et al. - The Examiner rejects claim 3 on the basis that a seventh reference, Lamikanra et al., which allegedly, as stated in the Office Action teaches targeting E7 of the human papilloma virus as a target antigen of treating tumors of interest. It is respectfully submitted by Applicants that this seventh cited reference that is used for a teaching (together with the other six references), fails to render obvious claim 3 for the same reasons argued above by Applicants (that the previous six references are not believed to be a proper combination for a rejection of obviousness). That is, Lamikanra et al. does not remedy the deficiencies discussed above with respect to claim 1.

In addition, the Lamikanra et al. reference similarly fails to disclose or suggest the features recited in claim 3. For example Applicants' invention as advanced in claim 3 calls for a fusion transcription unit which encodes an E7/ecdCD40L fusion protein which is not disclosed in Lamikanra.

NEW CLAIMS

New claims 35-39 are dependent from claim 1 and similarly are also believed to be allowable for at least reasons similar to those advanced above with respect to claim 1.

New independent claim 40 and dependent claims 41 and 42, are, in addition, similarly believed to be allowable. Accordingly, allowance of claims 35-42 is respectfully requested.

CONCLUSION

It is respectfully submitted for the reasons advanced above that all of the claims in the elected Group I, as well as the newly added claims, are not obvious in view of the cited art. Therefore all of the claims are believed to be allowable and are in condition for allowance.

To the extent necessary, a petition for an extension of time under 37 CFR 1.136 is hereby made. Please charge any shortage in fees due in connection with the filing of this paper, including extension of time fees, to Deposit Account 50-4752 and please credit any excess fees to such deposit account.

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